ADHESIVE COMPOSITIONS FOR SURGICAL USE

The present invention relates to new adhesive compositions comprising compounds resulting, for example, from the condensation of a carboxylic diacid with a sulphur-containing amino acid or one of its derivatives. These products contain reactive thiol SH functions which may oxidize to form disulphide bridges, leading to polymers which may or may not be crosslinked.

Biodegradable synthetic oligomers and polymers are already known, which very often consist of simple hydrolysable (ester or amide) chains of compounds capable of being degraded, forming metabolites.

Thus, Patent Application EP 0,332,530 describes hydrophilic polymers with a degree of polymerization of less than 1000, preferably between 20 and 300, and which consist of the polyamides resulting from the condensation of citric acid with diamines, such as lysine, cystamine and cystine.

The synthesis of these polyamides presents real difficulties associated with the protection and then the deprotection of citric acid.

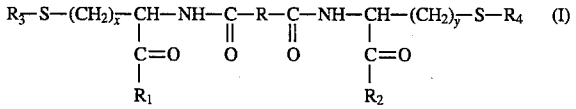
These biodegradable polyamides may be used for the preparation of medicament carriers, sutures, ligatures or prostheses, or alternatively of surgical adhesives.

If, for certain applications, the use of polymers of relatively high mass, of the type of those described in Patent Application EP 0,332 530, is advantageous for other uses, the use of monomers or oligomers bearing reactive or polymerizable functions (prepolymers) is preferable. This is particularly the case in reparatory surgery (bone-filling, surgical cements, biological adhesives etc.) or in dental surgery (dental cements etc.). In these applications, it is advantageous for the monomer or prepolymer to be able to defuse very readily into the tissue to be repaired and thus to penetrate into all the interstitial spaces. The polymerization may then occur "in situ" and give rise to an interlocking of the polymer chains which have the desired filling, cohesion or adhesion properties.

In this state of the art, one of the essential aims of the invention is to provide synthetic organic products which are biocompatible and biodegradable surgical adhesives based on non-toxic products.

Another essential aim of the invention is to provide such products comprising synthetic organic products which are found in the form of prepolymers and/or monomers, capable of diffusing readily into biological tissues and of polymerizing in situ, or even in vivo, in order satisfactorily to ensure the adhesion functions.

These aims and others are achieved by the present invention which relates, in the first place, to a biocompatible, biodegradable and non-toxic adhesive composition for internal or external surgical use, which comprises an organic product containing at least two thiol functions or derivatives and carboxylic functions, which may be protected or unprotected, and/or carbonyl functions, of the following general formula:

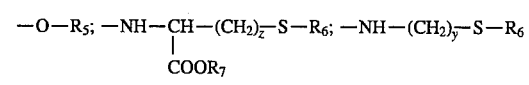


(I)

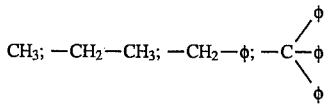
in which:

R is a hydrocarbon, preferably alkylated, chain containing from 1 to 50 carbon atoms and even more preferably an aliphatic chain having from 1 to 10 carbon atoms,

R_1 and R_2 are identical or different and are chosen from the following groups:



R_3, R_4, R_5, R_6 and R_7 independently represent hydrogen or an aliphatic and/or alicyclic and/or aromatic group, preferably a lower alkyl group and/or an aromatic group and, even more preferably, one of the following groups:



x, y and z=1 or 2.

For reasons of simplicity, the aromatic rings are denoted by the Greek letter ϕ throughout the present account.

In the sense of the present invention, the term "lower alkyl" denotes radicals containing from 1 to 6 carbon atoms.

The biological compounds corresponding to this formula advantageously have a relatively low molecular weight (less than 2000) and may thus diffuse readily through the protein networks (collagen, elastin etc.) or glycoprotein networks constituting the tissues. This is a property which it is advantageous to exploit in the field of adhesives.

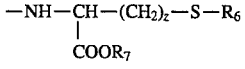
A first sub-class of the products used in the context of the invention comprises those in which the radicals R_1 and R_2 represent OR_5.

Even more precisely, when R_3 and R_4 correspond to hydrogen, this gives an oligomer which has, at each of its two ends, an SH function borne by a cysteine unit or derivative ("di SH" oligomer).

These SH functions have the capacity to react with themselves, in order to form disulphide bridges and to allow long chains to be obtained. This property may be exploited in order to prepare various adhesive products such as threads, films or viscous solutions which are biodegradable.

The presence of carboxylic functions on these di SH compounds makes it possible to envisage interactions with other molecules (for example natural macromolecules). This tends towards an improvement in the adhesive properties. In addition, these carboxylic functions lead to a hydrophilic nature and a capacity to bind active principles.

A second sub-class which is typical of the products used in the context of the invention regroups the products corresponding to the general formula indicated above, in which the radical R_1 represents:



and R_2 represents —O—R_5 or vice versa.

When R_5 and R_6 consist of hydrogen, these oligomer compounds may be termed as "tri SH" oligomers. These oligomers, the SH ends of which are capable of reacting to form disulphide bridges, allow possibilities of development of multidirectional networks to be glimpsed, which can improve the mechanical properties, the virtues of adhesion and the resistance to biodegradation of the products according to the invention.

A third sub-class of organic products which are used in the context of the invention consists of the products in which the radicals R_1 and R_2 consist of the radical: